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EXAMINER	
KRSEK STAPLES, J.	
ART UNIT	PAPER NUMBER
1813	18

DATE MAILED: 04/18/95

Below is a communication from the EXAMINER in charge of this application

COMMISSIONER OF PATENTS AND TRADEMARKS

ADVISORY ACTION

☑ THE PERIOD FOR RESPONSE:

a) ☑ is extended to run 6 months or continues to run _____ from the date of the final rejection

b) ☐ expires three months from the date of the final rejection or as of the mailing date of this Advisory Action, whichever is later. In no event however, will the statutory period for the response expire later than six months from the date of the final rejection.

Any extension of time must be obtained by filing a petition under 37 CFR 1.136(a), the proposed response and the appropriate fee. The date on which the response, the petition , and the fee have been filed is the date of the response and also the date for the purposes of determining the period of extension and the corresponding amount of the fee. Any extension fee pursuant to 37 CFR 1.17 will be calculated from the date of the originally set shortened statutory period for response or as set forth in b) above.

☑ Appellant's Brief is due in accordance with 37 CFR 1.192(a).

☑ Applicant's response to the final rejection, filed 3-15-95 has been considered with the following effect, but it is not deemed to place the application in condition for allowance:

1. ☐ The proposed amendments to the claim and /or specification will not be entered and the final rejection stands because:

   a. ☐ There is no convincing showing under 37 CFR 1.116(b) why the proposed amendment is necessary and was not earlier presented.

   b. ☐ They raise new issues that would require further consideration and/or search. (See Note).

   c. ☐ They raise the issue of new matter. (See Note).

   d. ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal.

   e. ☐ They present additional claims without cancelling a corresponding number of finally rejected claims.

   NOTE: _____

2. ☐ Newly proposed or amended claims _____ would be allowed if submitted in a separately filed amendment cancelling the non-allowable claims.

3. ☑ Upon the filing an appeal, ~~the proposed amendment ☐ will be entered ☐ will not be entered and~~ the status of the claims will be as follows:

   Claims allowed: _____
   Claims objected to: _____
   Claims rejected: 1,2

   However;

   ☐ Applicant's response has overcome the following rejection(s): _____

4. ☑ The ~~affidavit, exhibit or~~ request for reconsideration has been considered but does not overcome the rejection because (see attached)

5. ☐ The affidavit or exhibit will not be considered because applicant has not shown good and sufficent reasons why it was not earlier presented.

☐ The proposed drawing correction ☐ has ☐ has not been approved by the examiner.

☑ Other PTO 892 + refs. enclosed

PTOL-303 (REV. 5-89)

It is noted that the rejection under 35 U.S.C. § 101 was withdrawn in the Advisory Action dated 2/22/95 (see section under box number 3 titled "Applicant's response has overcome the following rejections"). Therefore, Applicant's arguments concerning this rejection are considered moot.

Regarding the rejection under 35 U.S.C. § 112, first paragraph, Applicant argues that it is the Examiner's burden to make a *prima facie* showing that the subject matter is not enabled. Applicant states that Example 8 in the specification describes the dosage and timing of the administration of Recognin to human or animals. Applicant argues that a person need only follow the steps in the application in order to practice the invention. Applicant states that the Examiner doubts that these steps will actually result in protective immunity and that this is really a utility argument and not an enablement argument. Applicant argues that working examples are not required to enable the subject matter. Applicant states that it is the Examiner's burden to show that a person of ordinary skill who follow the Applicant's clearly delineated instructions will fail and that the Examiner has not met this burden. Applicant submits that because actuarial studies have shown that the length of survival of known cancer patients correlates with serum level of anti-Recognin, together with the *in vitro* evidence of the cytotoxicity of the anti-Recognin antibodies to cancer cells, is compelling evidence that the disclosure is enabling.

Applicant's arguments have been considered but are not deemed to be persuasive. It is maintained that the specification does not teach how to use Recognin to inhibit or destroy clinical cancer. While the specification discloses dosages and the timing in which Recognin may be administered, it provides no evidence that administering the vaccine according to this protocol

will result in the inhibition or destruction of clinical cancer as claimed. Applicant continues to argue that the cytotoxicity data in the specification and the actuarial data discussed in Applicant's previous responses is compelling evidence that the disclosure is enabling. It is maintained, as previously stated, that the cytotoxicity of the anti-Recognin antibody to cancer cells *in vitro* is not sufficient to demonstrate that the administration of the Recognin would result in the treatment of cancer because the cytotoxicity measured *in vitro* cannot be extrapolated to the treatment of tumors *in vivo* where other factors such as the anatomical location of the tumor, the tumor mass, and the long tumor-host relationship make the *in vivo* system much more complex and unpredictable. Regarding the statistical correlation of naturally occurring anti-Recognin antibodies in cancer patients with survival, it was stated on page 5 of the Office Action dated 12/28/94 it is not clear whether the antibodies themselves are capable of treating or preventing cancer or whether other factors may be involved. This argument is supported by Zar (p 278 of *Biostatistical Analysis*) who states the following:

> "Although we have assumed a mathematical dependence of Y on X, we must not automatically assume that there is a biological cause and effect relationships. Causal relationships are concluded only with some insight into the natural phenomenon being investigated and may not be declared by statistical testing alone. Indeed, it is often necessary to determine the interrlationships between the two variables under study and other variables, for an observed dependence may, in fact be due to the influence of one or more additional variables."

In addition, in Applicant's publication of the actuarial data (Bogoch et al, Protides Biol Fluids 31:739-747, 1984) it was stated that "However, it does not necessarily follow that because an

antibody *in situ* is shown to be related to survival that replacement or increase of the concentration of that antibody by means of either classical methods or either active or passive immunotherapy will be clinically effective against cancer" (p 746).

In conclusion, it is maintained that it has not been determined whether anti-Recognin antibodies generated by the administration of Recognin are capable of preventing or inhibiting tumor growth *in vivo* due to the complicated *in vivo* system. In addition, it is not known whether the survival observed in patients with anti-Recognin antibodies is due to the antibodies or a combination of other factors. Therfore, it is not predictable whether antibodies generated by the administration of Recognin would result in the inhibition or destruction of cancer.

JKS
Julie Krsek-Staples, Ph.D.
April 13, 1995

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